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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/502,426	02/11/2000	Ricardo Azpiroz	11696-069001/2008-55300-	5144
26191	7590	02/04/2004	EXAMINER	
FISH & RICHARDSON P.C. 3300 DAIN RAUSCHER PLAZA 60 SOUTH SIXTH STREET MINNEAPOLIS, MN 55402			MEHTA, ASHWIN D	
			ART UNIT	PAPER NUMBER
			1638	

DATE MAILED: 02/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/502,426	AZPIROZ ET AL.	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 October 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 58-80,82-89 and 91-132 is/are pending in the application.
- 4a) Of the above claim(s) 124 and 126 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 88 and 89 is/are allowed.
- 6) ☒ Claim(s) 58-61,63-70,72-79,82-87,91-123,125 and 127-132 is/are rejected.
- 7) ☒ Claim(s) 62,71 and 80 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>10282003</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. The re-submission of Figure 8, as requested in the Office action mailed May 19, 2003, is acknowledged.
3. The rejection of claim 90 under 35 U.S.C. 101 is withdrawn, in light of its cancellation.
4. The rejection of claims 91-94 under 35 U.S.C. 112, 2nd paragraph, is withdrawn in light of the claim amendments.

Drawings

5. Applicants' reply does not contain corrections to the drawings required in Form PTO 948, which was attached to the Office action mailed May 19, 2003. Applicants are reminded that drawing corrections are required to be submitted within the time period set for the Office action to which it is attached. Drawing corrections are required to be submitted within the time period set for reply to the instant Office action.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

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Drawing changes must be made by presenting replacement figures which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments, or remarks, section of the amendment. Any replacement drawing sheet must be identified in the top margin as "Replacement Sheet" and include all of the figures appearing on the immediate prior version of the sheet, even though only one figure may be amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheets must be clearly labeled as "Annotated Marked-up Drawings" and accompany the replacement sheets.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

Election/Restrictions

6. Newly submitted claims 123 (in part), 124, and 126 are directed to an invention that is independent or distinct from the invention originally claimed and elected for the following reasons: the claims are drawn to an isolated polynucleotide comprising a nucleic acid encoding a polypeptide having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO: 2, and 60% or greater sequence identity to domain B of SEQ ID NO: 2, wherein said polypeptide is effective for modulating one or more phenotype traits (listed in claim 123). "Modulating one or more

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phenotypic traits” encompasses both increases and decreases of the traits. The isolated polynucleotides of the elected and examined invention do not cause a decrease in any of the phenotypic traits listed in claim 123. The isolated polynucleotides of claim 123 encompasses those that encode polypeptides that do not have the same function as those encoded by the polynucleotides of the elected and examined invention, and are therefore a different invention.

Applicant has received multiple actions on the merits for the originally presented and elected invention. This invention has been elected for prosecution on the merits. Accordingly, claims 124 and 126 will be withdrawn from consideration as being directed to a non-elected invention. Claim 123 will be examined to the extent that it reads on the elected and examined invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Information Disclosure Statement

7. The citations designated “AC” and “AI” in the IDS submitted October 28, 2003 were lined through, only because they already appear in, and initialed by the Examiner in, the IDS submitted October 18, 2001.

Claim Objections

8. Claims 62, 71, and 80 remain objected to for being dependent upon a rejected base claim.

Claim Rejections - 35 USC § 112

9. Claims 58-61, 63-70, 72-79, 82-87, and 91-94 remain and new claims 95-123, 125, and 127-132 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written

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description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record stated in the Office action mailed May 19, 2003. Applicants traverse the rejection in the paper submitted October 28, 2003. Applicants' arguments were fully considered but were not found persuasive.

Applicants argue that page 25 of the specification defines "DWF4 polypeptide" to include a polypeptide that functions in the brassinolide (BL) biosynthetic pathway and that the term encompasses mutants and fragments of the native DWF4 sequence so long as the protein functions for its intended purpose. Applicants argue that pages 40-41 of the specification sets forth methods to detect enzyme activity, that pages 41-42 describe a characteristic DWF4 phenotype as including any activity that is exhibited by the native DWF4 polypeptide, and that page 42 lists DWF4 activities. Applicants argue that pages 67-71 set forth growth and feeding experiments to identify enzymatic activities in biosynthetic BR pathways (response, paragraph bridging pages 15-16).

Claims 58, 67, 76, 85-87, and 123 encompass isolated polynucleotides encoding polypeptides having greater than 43% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2, 60% or greater sequence identity to domain A of SEQ ID NO: 2, and 60% or greater sequence identity to domain B of SEQ ID NO: 2. The polypeptides are effective for catalyzing the hydroxylation of campestanol or 6-oxocampestanol, or increase one or more of the phenotypic traits listed in claim 123. Wide variation in structure is expected among the species of polynucleotides encompassed by the claims. The polypeptides encoded by the claimed

polynucleotides can differ from SEQ ID NO: 2 in as many as 293 amino acids. The specification discloses a single amino acid sequence, SEQ ID NO: 2 that catalyzes the hydroxylation of campestanol and 6-oxocampestanol. The specification does not disclose what amino acids of SEQ ID NO: 2 can be altered such that the resultant amino acid sequences have at least 43% identity with SEQ ID NO: 2, and 60% identity to domains A and B of SEQ ID NO: 2, and retains its functional activity. The DWF4 characteristics on pages 41-42 and the growth and feeding experiments on pages 67-67 do not describe the amino acid residues of SEQ ID NO: 2 that may be changed without altering its functional activity.

Applicants argue that page 18 of the specification states that polynucleotides or polypeptides of the invention can demonstrate various percentage ranges of sequence identity “over a defined length of the molecules.” (response, page 16, 1st full paragraph). However, this does not describe the amino acid sequences themselves. The specification does not describe the portion of the molecules that is referred to by the “defined length of the molecules.” Applicants argue that pages 42 and 43 note that a DWF4 analog can be a derivative, fragment, or fusion of native DWF4 polypeptides, that derivatives can include changes within domain, motifs, or consensus regions, and analogs that increase sterol binding (response, page 16, 1st full paragraph). However, again, the only amino acid sequence disclosed in the specification to be correlated with 22 α -hydroxylase activity is SEQ ID NO: 2.

Applicants argue that Example 3 in the specification describes four characteristic domains of P450 proteins (response, paragraph bridging pages 16-17). However, P450 proteins that do not have the 22 α -hydroxylase activity of SEQ ID NO: 2 also have these domains. The presence of these domains alone does not identify a protein as having the 22 α -hydroxylase of

SEQ ID NO: 2. Applicants continue, arguing that Example 3 also discusses the classification of P450 proteins based on sequence identity, that such a system was well known to those of ordinary skill in the art, citing Nebert et al. (DNA and Cell Biology, Vol. 10, 1991). Applicants argue that a P450 protein sequence from one gene family is defined as having $\leq 40\%$ identity to that from another family. Sequences sharing between 40% and 55% are in different subfamilies, and sequences having greater than 55% identity are in the same subfamily (response, paragraph bridging pages 16-17). However, this system for placing P450 genes in different families and subfamilies was arbitrarily made. Nebert et al. teach that defining P450 proteins sequences from one gene family as having $\leq 40\%$ identity to those of other families is arbitrary (page 2).

Furthermore, it is only mammalian sequences having more than 55% identity that are placed in the subfamily (Nebert et al., page 2). More importantly, it is noted that this classification system does not consider protein activity when making assignments. Nelson et al. (Pharmacogenetics, 1996, Vol. 6, pages 1-42) discusses updates on P450 sequences and the nomenclature system. Nelson et al. emphasize that similarities in enzymatic activities *cannot* be used to classify genes within any gene family or subfamily (page 4). Assignments of claimed isolated polynucleotides into gene families or subfamilies using the system referred to by Applicants, apparently does not correlate the structure of the claimed polynucleotides with their function.

Applicants continue, arguing that the present claims recite that the polypeptides 60% or greater sequence identity to domains A and B of SEQ ID NO: 2, thus requiring higher than subfamily level of sequence identity (response, page 17, 1st full paragraph). However, the P450 nomenclature system does not indicate that proteins are placed in the same subfamily if domains A and B, as opposed to sequence identity of the entire protein, have greater than 55% identity.

Further, there is no written descriptive support in the specification for the recitations “60% or greater sequence identity to domain A (or B) of SEQ ID NO: 2”, or the ranges of percent sequence identities to domain A or B recited in claims 127-132.

10. Claims 58-61, 63-70, 72-79, 82-87, 91-123, 125, and 127-132 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 58, 67, 76, 85-87, and 123 contain the recitations, “60% or greater sequence identity to domain A of SEQ ID NO: 2” and “60% or greater sequence identity to domain B of SEQ ID NO: 2”. Claims 127-132 recite other ranges of percent identity to domain A or B of SEQ ID NO: 2. The specification at pages 53-54 discusses domains A and B of P450 proteins and of SEQ ID NO: 2. Figure 3 shows domains A and B of SEQ ID NO 2 and of other P450 proteins. However, there is no written descriptive support for the aforementioned claim recitations in the specification. The discussions of the domains in the specification do not mention percent sequence identities shared among different proteins. The recitations are **NEW MATTER** and must be removed from the claims.

11. Claims 58-61, 63-70, 72-79, 82-87, and 91-94 remain and claims 95-123, 125, and 127-132 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides encoding SEQ ID NO: 2, plant host cells, transgenic plants

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comprising a polynucleotide encoding SEQ ID NO: 2, method of making a transgenic plant comprising introducing into a plant a polynucleotide encoding SEQ ID NO: 2, and a method for producing a polypeptide in plant cell comprising providing a plant host cell comprising introducing a polynucleotide encoding SEQ ID NO: 2, does not reasonably provide enablement for polynucleotides that do not encode SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record stated in the Office action mailed May 19, 2003. Applicants traverse the rejection in the paper submitted October 28, 2003. Applicants' arguments were fully considered but were not found persuasive.

Applicants argue that they have claimed only those polynucleotides that encode polypeptides having the recited structural limitations and maintain a particular function. Applicants also argue that the claims recite higher than subfamily sequence identity for domains A and B (response, paragraph bridging pages 18-19). Applicants argue that the specification sets forth methods to detect enzymatic activities of polypeptides, growth and feeding experiments, methods of making transformed plants (response, page 19, 1st full paragraph). However, the specification does not teach how to make the claimed polynucleotides that encode proteins that differ from SEQ ID NO: 2 and which still retain its functional activity. The specification does not teach what amino acids one skilled in the art is to change to produce the claimed products. SEQ ID NO: 2 has 513 amino acid residues. The polypeptides encoded by the claimed polynucleotides may differ from SEQ ID NO: 2 in as many as 293 of these residues. What changes will not also change the 22 α -hydroxylase activity of SEQ ID NO: 2 is not taught.

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Undue experimentation would be required by one skilled in the art to determine which 293 residues of SEQ ID NO: 2 to change, and what to change them to, to yield a protein in which the functional activity has not been altered. Further, as discussed above, Nelson et al. emphasize that the P450 nomenclature system does not consider enzyme activity when assigning P450 sequences to families and subfamilies. The nomenclature system of the prior art also does not mention anything concerning the sequence identities of domains A and B, or domains C and D, when assigning proteins to families. Further, domains A and B, along with domains C and D, are conserved domains that appear in all P450 proteins. No evidence has been presented showing that P450 proteins that share a sequence identity above a certain percentage in these domains will also have the same functional activity.

Summary

12. Claims 88 and 89 are allowed. Claims 62, 71, and 80 are objected. Claims 58-61, 63-70, 72-79, 82-87, 91-123, 125, and 127-132 are rejected. Claims 124 and 126 are withdrawn from consideration.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this or earlier communications from the examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The examiner can normally be reached on Mondays-Thursdays and alternate Fridays from 8:00 A.M to 5:30 P.M. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 and 703-872-9306 for regular communications and 703-872-9307 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

January 30, 2004

A handwritten signature in black ink, appearing to read 'Ashwin D. Mehta', is written over a horizontal line.

Ashwin D. Mehta, Ph.D.
Primary Examiner
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